Reports

This part of the EJRR hosts reports in which our correspondents keep readers up to date on the most recent developments in different areas of risk regulation. Our aim is to fuel the debate and trigger future research on cutting-edge risk subjects. The Reports are organised under different policy sections. Further sections will be added at regular intervals. If you are interested in contributing to any of the existing sections, please contact the Reports Editor at enrico.bonadio.1@city.ac.uk

Biotechnology

This section aims to update readers on decisions related to marketing products of modern biotechnology (e.g., GMOs, animal clones) at EU level and on national measures concerning their production. Special attention is devoted to problems of competence between Member States and the EU in regulating biotechnology issues; the institutional dynamics of decision making regarding products derived from modern biotechnology; the relationship between the EFSA and the EU institutions on green biotech-related issues; the evolution of EU regulatory framework and of national attitudes towards the risks and benefits of biotechnology derived products and their production. This section will also delve into the interaction between the EU legislation and WTO law regarding advances in the application of biotechnology within the agri-food value chain.

Biosimilars: Current situation and future expectations

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I. Biosimilars definition. Global need for biotherapeutics

Biotherapeutics, also known as biomedicines, biopharmaceuticals or biotechnology products, can be used for the augmentation or replacement of naturally occurring proteins in numerous pathological conditions, including common diseases and rare genetic conditions. Currently, the two mature biotherapeutic sectors are recombinant protein therapeutics (rDNA proteins) and monoclonal antibodies (mAbs), which are set to generate more than 90% of total sales from 2010–2015. Examples of biotherapeutics include human erythropoietin (Erypo®), human insulin (Humulin®), rituximab (Rituxan®), human growth hormone (Genotropin®) and tumor necrosis factor-alpha blockers such as adalimumab (Humira®), etanercept (Enbrel®) and infliximab (Remicade®). Despite the fact that they represent one of the most dynamic and promising segments of the pharmaceutical industry and an impressive contribution in health care, patient access to these products is often limited by their high costs, particularly in developing countries. It has been reported that the cost of these products, which can range from $15,000 to $100,000 per year of treatment, is much higher than the cost of traditional small-molecule products, which implies important economic challenges to guarantee their affordability.

The increasing focus on cost containment and the expiration of patents for the first major group of originator’s biotherapeutics have preceded the emergence of products that are designed to be “similar” to a licensed originator or innovator product. Several terms, such as “biosimilar products”, “follow-on protein products”, “similar biological medicinal products” and “subsequent-entry biologics” have been employed by different jurisdictions to describe them. Biosimilars have been defined as products that are

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similar but not identical, in terms of quality, safety and efficacy to an approved biological product. That allows the applicant to rely on certain existing scientific knowledge about the biological medicine that has already been authorized4.

II. EU Biosimilar Guidelines

The concept of “Similar Biological Medicinal Products” was introduced in Europe in 2003 by the amendment to Annex I of Directive 2001/83/EC, setting the legal basis for its marketing authorization5. Since then, the EMA (European Medicines Agency) has published specific guidelines on similar biological medicinal products containing recombinant somatropin6, granulocyte-colony stimulating factor7, insulin8, erythropoietin9, interferon alpha10 and low-molecular-weight-heparins11 while concept papers for similar biological medicinal products containing recombinant interferon beta12, follicle stimulating hormone13 and monoclonal antibodies are already available14.

According to the regulatory guidelines developed for the European Union one of the key paradigms for biosimilars is that the clinical data required at approval are limited. This is an important issue since it represents a significant reduction in development costs, making biosimilars production a viable business. Nonetheless, and because of the potential risks associated with biotherapeutic products, there is a need for a rigorous risk management plan and pharmacovigilance program with respect to efficacy and safety during the post-approval period.

Another important aspect in biosimilars approval process relies on therapeutic indications, which may be extended if justified. EMA accepts that if the biosimilar shows adequate comparability to the innovator or original product for one indication, it is reasonable to extend the approval of the biosimilar to other indications of the innovator product. That is important in order to select the most sensitive conditions for the design of a comparative trial. Omnitrope (marketed by Sandoz) is a biosimilar version of the reference product Genotropin (manufactured by Pfizer). Like Genotropin, Omnitrope is a recombinant human somatropin produced from E. coli. The EMA approval of this biosimilar included indications for which it has not been evaluated in clinical trials, based on extrapolation of data from the reference product. Thus, the comparability of Omnitrope to Genotropin was demonstrated in a randomized controlled trial in children with lack of growth hormone with an additional safety study performed also in children, while the approval of Omnitrope included extrapolation of these clinical data to adults with pronounced growth hormone deficiency15.

Nowadays, there are more than ten biosimilar products in the European market without reports of adverse incidents and it has been estimated by the European Generic Medicines Agency that biosimilars savings in the European Union were around €1.4 billion in 200916. Nevertheless, demonstrating bio-

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similarity is not simple and it has been reported that the average cost of bringing a biosimilar to a highly-regulated market is around 75–250 million$^{17}$. Head-to-head studies must be run, that is comparison to the reference product including both physicochemical and functional characterization data in addition to non-clinical and clinical data. A comparability exercise needs to demonstrate that the biosimilar and the reference product have similar profiles with respect to product quality, safety and efficacy. That is accomplished through analytical studies, examining physical properties, aminoacid sequence, high order structures and post-translational modifications.

*In vitro* or *in vivo* potency assays must demonstrate comparable activity and additionally levels of product related and process related impurities need to be assessed and quantified.

If differences are present between the biosimilar and the reference biologic product on product impurity and stability profile, these differences have to be justified using scientific knowledge or preclinical or clinical studies. Also, clinical studies should be designed to demonstrate equivalence rather than non-inferiority, i.e., a "better" outcome is not an option because it indicates lack of similarity.

Moreover, in some cases the Committee for Medicinal Products for Human Use of EMA had adopted a negative opinion on the Marketing Authorization Application presented by a biosimilar sponsor on the grounds of major concerns on quality issues or non-clinical issues. In such circumstances, this organism recommended the refusal of the marketing authorization since there were differences identified in the impurity profile between the two products, insufficient stability data, and inadequate validation of manufacturing process for the drug product or different response in clinical trials$^{18}$. In other cases the application was withdrawn by the sponsor after day 120 of the Centralized Procedure. At this point the company is expected to respond to the list of questions and objections drafted during the assessment process by the Committee for Medicinal Products for Human Use$^{19}$.

### III. Worldwide situation

Biosimilars have been in the market of several countries like Argentina, India, Brazil, Mexico among many others for a long time. This has been extraordinary useful for facilitating patient access to numerous disease treatments with biotherapeutics. It has occurred thanks to an adequate legal framework on intellectual property, specific of each country, and in certain cases by virtue of an important local scientific development and recombinant protein manufacturing skills. It is clear that the decision on biosimilar use and regulation can only be taken at a national or possibly regional level. In 2009, a WHO Expert Committee on biological Standardization issued guidelines, largely based on EMA’s guidelines, to promote global consensus on the regulation of biosimilars, assist in their registration based on an abbreviated regulatory process taking into account the claim of similarity to a reference product and in this manner improve the availability of safe and effective biosimilar products worldwide$^{20}$. There is no doubt about EMA’s pioneering work to introduce a regulatory framework for biosimilars and to facilitate market entry and competition for off patent medicines. This has provided also a scientific approach to avoid unnecessary risks for patient safety and unnecessary or even unethical animal or humans trials. On this basis other country regulatory authorities have developed their own guidelines for biosimilars approval. That is the case of Japan, Canada, Switzerland, Turkey and Brazil. In Australia, for example, the EMA guidelines were adopted without changes.

The United States is still in the process of implementing a regulatory pathway for biosimilars, or follow-on biologics as they have been specifically named in that country. The Food and Drug Administration (FDA) is the authority that accepts, reviews and approves license applications for biosimilar products, and is working to establish procedures and create a mechanism to review applications. Recently, three draft guidance documents have been published in order to clarify expectations and provide predictability to sponsors initiating biosimilar

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Biotherapeutic product manufacturers sometimes may need to introduce changes in the manufacturing process that is used to make a particular product. These changes can be driven for a variety of reasons, including improvements of product quality, yield, and manufacturing efficiency. Typical examples are increasing manufacturing scale due to increased demand, improving product stability through changes in formulation, replacement of master cell bank, replacement of raw materials which are no longer available, changes in the purification process and removal of animal derived components from the process.

All this can result in alterations in product quality that can be minor or major depending on the extent of the manufacturing change.

IV. Comparability concept

Biotherapeutic product manufacturers sometimes may need to introduce changes in the manufacturing process that is used to make a particular product. These changes can be driven for a variety of reasons, including improvements of product quality, yield, and manufacturing efficiency. Typical examples are increasing manufacturing scale due to increased demand, improving product stability through changes in formulation, replacement of master cell bank, replacement of raw materials which are no longer available, changes in the purification process and removal of animal derived components from the process.

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In 1996 the FDA was the first regulatory authority to provide a mechanism to evaluate the impact of these changes without performing additional trials. It published the Guidance “Demonstration of Comparability of Human Biological Products, including Therapeutic Biotechnology-derived Products” which stipulates that comparability assessment is required to support manufacturing process changes without performing additional clinical studies to demonstrate safety and efficacy. A hierarchical risk-based approach is recommended, starting with an extensive “comparability exercise”. That includes analytical comparison of post-change product and pre-change product, followed by biological characterization and, if needed, in vivo pharmacokinetic (PK), pharmacodynamics (PD), safety and/or efficacy studies. The need for an in vivo study and the type of study required will depend on the magnitude and the potential impact of the changes. In other words, regulatory pathways imply that comparability exercise for postchange products is expected to cover a complete physicochemical and biological analysis followed by preclinical and clinical studies on a case by case basis. If the quality attributes of a product after a manufacturing change deviate from those of pre-change product, this should increase pre-clinical and clinical study requirements. On the contrary, when a product remains within approved specifications after a change, it suggests that the pre- and post-change products are comparable and therefore the changes in the manufacturing process can be made without additional preclinical or clinical studies. Thus, according to FDA the term “comparable” applies to a product after a manufacturing change to an already approved product.

These concepts were extended by EMA with minimal modifications from process changes and product changes made by one company to comparable products produced by a different sponsor. In this case the product is called biosimilar, and it must undergo a comparability exercise with the reference product using a range of biological, physicochemical and immunological procedures.

Some biosimilar proponents also rely on the concept of changes on product quality to argue that the “goalposts” for biosimilarity should be based on the variability of innovator products over time and across batches. They also advocate for a case-by-case approach to approval, rather than product or even biosimilar-wide standards and rules. Even taking into account the recent advances in US regulations on biosimilarity determination some authors have pointed out the difficulties for biosimilars approval in US, mainly due to multiple restrictions for the abbreviated Biologic License Application (aBLA) pathway. The aBLA is an option for approval of biosimilars according to BPCI Act. It requires the disclosure and publication of the full dossier of the biosimilar manufacturer preparing the way for the innovator or even third parties (universities, other companies) to file infringement suits. In contrast, by filing through the full Biologic License Application (BLA) process, the biosimilar manufacturer’s dossier and other data remain proprietary and therefore the biosimilar manufacturer does not need to give the innovator (or anyone else) the full details of its filing nor manufacturing process. Moreover, since litigation from the innovator is not acceptable “without reasonable assertion”, without access to the full dossier or details of the biosimilar developer’s manufacturing process it is unlikely that the innovator (or other third party) is acquainted with the “reasonable assertion” requirement.

Despite these discussions, many experts predict that biosimilars business will grow significantly, mainly in developed countries. Revenue from the sale of biosimilars is expected to grow from $311 million in 2010 to $2.5 billion in 2015. With this lucrative market, it is no surprise that large pharmaceutical companies are giving signals of interest in these products. Some of these companies reached agreements with other enterprises with a strong knowhow in biosimilars development and production in concordance with well-built manufacturing expertise of required export quality. For example, Pfizer announced in October 2010 a strategic global agreement for worldwide commercialization of biosimilar insulin and analogous products with the
Indian biotechnology company Biocon. Under this agreement, Pfizer will make upfront payments totaling $200 million to Biocon for exclusive rights to the insulin and insulin analogous products globally, with certain exceptions\(^35\). Pfizer is not alone in its biosimilar intentions. Merck has also developed a biosimilar division, Merck BioVentures. Merck also plans to have five biosimilar programs in Phase III development by 2012\(^36\).

V. Concluding remarks

Many countries have already implemented a rigorous program based on scientific principles that evaluates the comparability of biosimilar and innovator products through analysis of molecular structure, biological activity, functional pharmacokinetic parameters, degradation profile and limited clinical trials.

Variations among batches of biopharmaceutical products are attributable to these products complexity and manufacturing processes changes over the product life cycle. The comparability exercise was introduced in the 90’s by the FDA to allow manufacturers of biological products to implement changes in the manufacturing process, in most cases without performing additional clinical trials. The EMA extended the scope of this comparability exercise to biological therapeutics produced by different manufacturers, creating a mechanism for comparability between originator and biosimilar products. If differences are present, regulatory processes intend to quantify and understand the effects, leading to the evaluation of requirements for clinical trials.

EU guidelines have resulted in the approval of more than ten biosimilars with comparable efficacy and safety profiles of their respective reference originator biotherapeutics. Moreover, additional biosimilar approvals are expected in Europe, not only in the classes where biosimilars are already approved, but in other classes, as monoclonal antibodies.

These precedents have been valuable in the process of approving biosimilars in the rest of the world, including the US. In this country biosimilar products have not been approved yet but new regulation opens the door for different biosimilar sponsors to present their applications. It is expected that the first biosimilars approved in the US will be those that are currently being sold in Europe, for which there is already significant clinical trial information and post marketing surveillance.

It is predictable an increase in the number of collaborations acquisitions and joint ventures between companies that want to access to the huge biosimilar market. These deals will permit companies to leverage pipelines and geographical presence, thereby driving overall commercial success of biosimilars in the future.

Finally, since a significant number of biosimilar products are already approved or are under development these agents will undoubtedly play an increasing role in disease management, providing access to high quality, safe and effective biotherapeutics.

The Product of Nature Doctrine in the Myriad Saga

Emanuela Gambini*


On March 26, 2012, the U.S. Supreme Court granted the petition for a writ of certiorari on Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al. (the “Myriad case”)\(^1\). This decision vacated the judgment of appeal and remanded the case to the United States Court of Appeals for the Federal Circuit for further consideration in light


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